Docket No.: 0649-1380PUS1
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Kazutaka IKEDA et al.

Application No.: 10/594,597 | Confirmation No.: 6839

Filed: September 28, 2006 | Art Unit: 1634

For: METHOD OF EVALUATING DRUG SENSITIVITY BY ANALYZING THE MU-OPIOID RECEPTOR GENE | Examiner: S. T. Kapushoc

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Madame:

I, Kazutaka IKEDA, do declare and state as follows:

1. I am a co-inventor of the instant application.

2. My *curriculum vitae* is enclosed, which describes my education and experience in molecular psychiatry and neuroscience.

Enablement of the Invention

3. I have reviewed the outstanding Office Action, which issued on May 15, 2009, and I am familiar with the rejections described therein. In particular, I have reviewed the rejection of the claims under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

4. The Examiner rejects the claims as lacking enablement, in part, because he believes that correlating polymorphisms with phenotypes is unpredictable. For the reasons set forth below, it is my opinion that an ordinary artisan would have recognized from the present

application that the polymorphisms described in the amended claims are reliably associated with a sensitivity to drugs, *i.e.*, methamphetamine, methylenedioxymethamphetamine, amphetamine, dextroamphetamine, dopamine, morphine, DAMGO, codeine, methadone, carfentanil, fentanyl, heroin, cocaine, naloxone, naltrexone, nalorphine, levallorphan, pentazocine, buprenorphine, oxycodone, hydrocodone, levorphanol, etorphine, dihydroetorphine, hydromorphone, oxymorphone, ethanol, methanol, diethyl ether and/or tramadol.

5. I have also reviewed the amendments to the specification submitted herewith. For the reasons set forth below, it is my opinion that the originally filed application supports the amendments.

6. The amended claims are directed to a method of evaluating sensitivity of an individual human subject to a drug, the method comprising: linking a gene polymorphism to individual drug sensitivity, the gene polymorphism selected from the group consisting of: IVS3 + A6151G of SEQ ID NO: 28; the gene polymorphisms described in Table 2 of SEQ ID NOS: 33-98 and 100; the gene polymorphisms of Table 6 comprising IVS3+A8449G of SEQ ID NO: 29, TAA+A2109G of SEQ ID NO: 39, and TAA+G2287A of SEQ ID NO: 41; wherein said Table 2 gene polymorphisms and/or said Table 6 gene polymorphisms are in linkage disequilibrium with IVS3 + A6151G of SEQ ID NO: 28; the drug being at least one member selected from the group consisting of methamphetamine, methylenedioxymethamphetamine, amphetamine, dextroamphetamine, dopamine, morphine, DAMGO, codeine, methadone, carfentanil, fentanyl, heroin, cocaine, naloxone, naltrexone, nalorphine, levallorphan, pentazocine, buprenorphine, oxycodone, hydrocodone, levorphanol, etorphine, dihydroetorphine, hydromorphone, oxymorphone, ethanol, methanol, diethyl ether and tramadol.

7. The present application teaches that the polymorphism described at position IVS3 + A6151G, which is specified in the amended claims, is associated with methamphetamine sensitivity at a significant value of P=0.0269, *see* Table 10, page 59 of the originally filed application.

8. Further, Table 6, as amended, describes that IVS3 + A6151G is in strong linkage disequilibrium with IVS3 + A8449G, *i.e.*, D'=1.000 and r^2=0.800. Accordingly, an ordinary artisan would have recognized that IVS3 + A8449G is also associated with drug sensitivity.

9. In further support thereof, Fukuda *et al.*, *PAIN®*, 2009, *in press,* of which I am a co-author, confirms the association of IVS3 + A8449G with drug sensitivity, *i.e.*, fentanyl, *see* Table 2 and Figures 3 below.

Table 2

Patients' demographic and clinical data

	All Patients		A118G (rs1799971	A118G (rs1799971	IVS+A8449 G (rs9384179)	IVS+A8449G (rs9384179)
			AA	AG + GG	AA	AG + GG
Age (years)	25.8 ± 7.4	(15-50)	25.6 ± 7.3	25.9 ± 7.5	25.9 ± 7.4	25.5 ± 8.1
Male/Female	97/183		34/52	63/131	71/148	26/35
Body weight (kg)	57.9 + 11.1	(38-128)	59.8±10.8	57.1± 11.2	57.2 ± 10.8	60.5 ± 11.8
PPLpre (s)	14 [9,23]	(2-150)	15 [10,27]	14 [8,22] (*)	14 [9,23]	15 [9,25]
PPLpost (s)	29 [16, 57]	(4–150)	34 [18, 89]	28 [16, 49] (*)	30 [16, 57]	28 [18, 85]
Analgesic effect (PPLpost–PPLpre) (s)	13 [5, 37]	(-17 to +143)	15.0 [6, 52]	12 [5, 33]*	13 [5, 36]	15 [4, 48]
Duration of anesthesia (min)	170 [157, 186]	(101–286)	171 [157,189]	169 [157,185]	170 [156, 186]	170 [162, 185]
Duration of surgery (min)	104 [91, 120]	(66–211)	105 [89,119]	103 [91, 121]	104 [91, 121]	105 [89, 117]
Total propofol dose (mg/kg)	25.0 [22.0, 27.9]	(5–42)	25.3 [22.4, 27.8]	25.0 [22.0, 28.2]	25.0 [22.0, 27.8]	25.5 [22.5, 28.7]
Preoperative fentanyl use (μg/kg)	2		2	2	2	2
Intraoperative fentanyl use (μg/kg)	3.9 [2.9, 5.3]	(0–13.6)	3.8 [2.9, 5.3]	3.9 [2.9, 5.3]	3.9 [2.9, 5.2]	3.8 [3.0, 5.6]
24-h postoperative fentanyl use (μg/kg)	2.3 [1.1, 4.1]	(0–13.8)	2.3 [1.1, 3.7]	2.3 [1.1, 4.3]	2.5 [1.3, 4.3]	1.5 [0.8, 3.4]*
Perioperative fentanyl use (μg/kg)	6.6 [5.0,8.6]	(0.8-24.0)	6.2 [5.0,8.1}	6.6 [5.0,8.7}	6.7 [5.2, 8.6]	6.0 [4.6,8.3] (*)
Total perioperative analgesic use (μg/kg)	7.5 [5.9, 9.5]	(1.8–25.3)	7.1 [5.8, 9.0]	7.6 [6.0, 9.6]	7.6 [6.1, 9.6]	6.9 [5.4,8.9] (*)
VAS pain score at 3 h (mm)	25 [13, 48]	(0–90)	25 [15, 50]	26 [12, 46]	26 [13.5, 50]	24 [10, 36]
VAS pain score at 24 h (mm)	25 [10, 40.5]	(0–83)	25 [9, 49]	25 [10, 40]	25 [10, 44.5]	25 [8, 36]

Data are expressed as numbers, mean ± SD (range), or median [interquartile range].
(*) $p < 0.1$, compared with subjects not carrying minor allele.

* $p < 0.05$, compared with subjects not carrying minor allele.

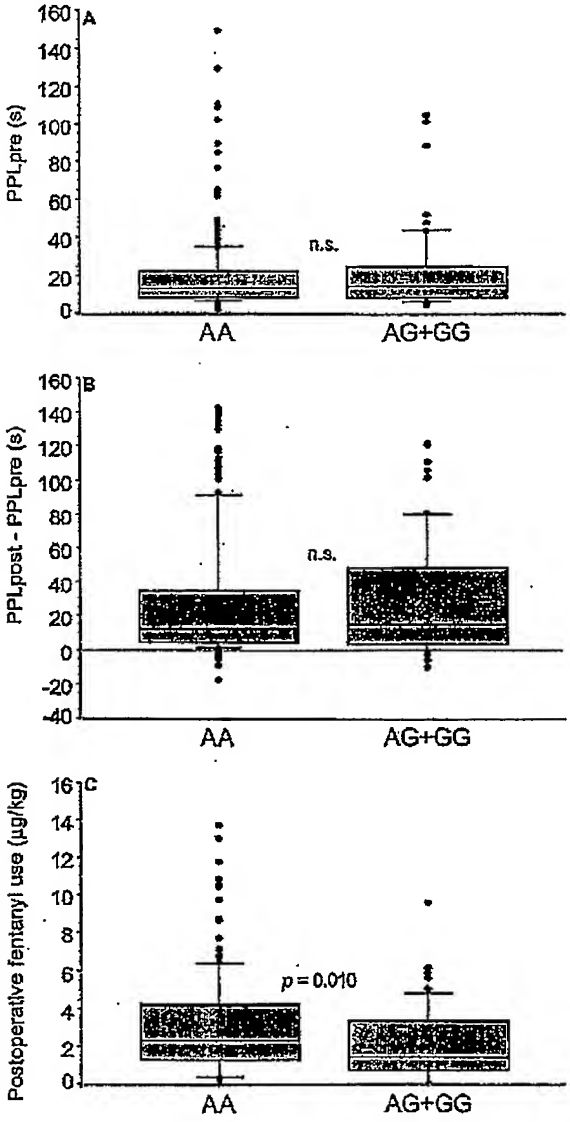

Fig. 3. Associations between genotypes of the IVS3+A8449G SNP (AA, n = 219; AG + GG, n = 61) and (A) baseline pain perception latency (PPLpre), (B) the analgesic effect of fentanyl in the cold pressor-induced pain test (PPLpost–PPLpre), and (C) 24-h postoperative fentanyl use. Data are expressed by box and whisker plots. Upper and lower ends of boxes represent the 75th and 25th percentiles. Whiskers represent the 90th and 10th percentiles, and filled circles represent outliers. The median is depicted by a solid line in the box.

10. In view of the above, an ordinary artisan would have recognized from the present application that IVS3+A6151G, and the polymorphisms in linkage disequilibrium with IVS3+A6151G, *e.g.*, the Table 6 polymorphisms described in the amended claims, such as IVS3 + A8449G, are also associated with sensitivity to the drugs specified in the amended claims.

11 Moreover, an ordinary artisan would have recognized from the present application that the gene polymorphisms described in Table 2, are also in linkage disequilibrium with IVS3 + A6151G, and, accordingly, are also associated with drug sensitivity. As described in Table 6 of the originally filed application, IVS3+A6151G is in strong linkage disequilibrium with TAA+A2109G and TAA+G2287A. These two polymorphisms of Table 2 are in linkage disequilibrium with the other gene polymorphisms described in Table 2 and with each other. Accordingly, an ordinary artisan would have recognized that all of the gene polymorphisms described in Table 2 are in linkage disequilibrium with IVS3+A6151G.

12. In view of the foregoing, it is my opinion that an ordinary artisan would have recognized from the instant application that the gene polymorphisms specified in the amended claims are predictably associated with sensitivity to the described drugs.

Support for Changes to the Specification

13. In addition, it is my opinion that the originally filed application supports the amendments to Tables 2, 4, and 6. Table 2 is amended to specify TAA+2008 and TAA+2025 in lieu of TAA+2007 and TAA+2026, respectively. Table 4 is amended to specify TAA+C2008T in lieu of TAA+C2007T. Table 4 is further amended to add the sequence corresponding to the gene polymorphism, TAA+G2025A.

14. In my opinion, the correct locations of the polymorphisms are inherent in the sequences. For example, an ordinary artisan would recognize that the C/T and G/A

polymorphisms in the 3' untranslated region of the mu-opioid receptor, initially described as 2007 and 2026 bases downstream of the stop codon, were incorrectly reported since an ordinary artisan would. have recognized from sequencing individual samples corresponding to the oligonucleotides containing the polymorphisms of, *e.g.*, Table 4, that the polymorphic positions are, in fact, 2008 and 2025 bases, respectively, from the stop codon in the mu-opioid receptor.

15. In addition, support for the new sequence corresponding to the gene polymorphism TAA+G2025A is inherently described in the present application. As explained, *e.g.*, on page 25 of the present application, oligonucleotides of, *e.g.*, 101 bases, having the polymorphism at base 51, were recognized as part of the invention. In addition, all of the 67 oligonucleotides of SEQ ID NOS: 33-98, of which the TAA+G2025A would be a part, are 101 bases with the polymorphism at position 51. Thus, one skilled in the art would readily recognize that the associated sequence for TAA+G2025A is that presented in SEQ ID NO: 100. An ordinary artisan, accordingly, recognizes the location of the TAA+G2025A in the mu-opioid receptor and the 50 nucleotides upstream and downstream of the polymorphism.

16. Table 6 is also amended to correct the format of 1.000 from the underlined format to a bold and italicized format at the intersection of the fifth line specifying IVS3+A6151G and the sixth row specifying IVS3+A8449G. Table 6 is further amended to correct the value 0.001 at the intersection of the sixth line specifying IVS3 +A8449G and the fifth row specifying IVS3+A6151G to 0.800, and to corect the format of the value at this position from plain text to bold and italicized text. These format changes indicate significant D' and r^2 values.

17. Support for the corrections to Table 6 are inherently supported by the present application. An ordinary artisan repeating the linkage disequilibrium analysis described in the present application, *e.g.*, on pages 27-31, would have determined that the initially reported D' and r^2 values were incorrect because both values, in fact, reach significance. Accordingly, the significance of the amended values is inherently supported.

18. In view of the above, it is my opinion that the amended tables are supported by the originally filed application.

STATEMENT UNDER 18 U.S.C. § 1001

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By: Kazutaka Ikeda
Kazutaka Ikeda

Date: November 15, 2009

Enclosure: Appendix (Curriculum Vitae)

CURRICULUM VITAE

(July 18, 2009)

Name, Family name:	Ikeda
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Date of birth:	February 1, 1966
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Education:

1985-1989	Faculty of Technology, University of Tokyo Awarded the degree of B. Eng.
1989-1992	Department of Neurochemistry, Osaka University Medical School Awarded the degree of M. Med.
1992-1995	Department of Neuropharmacology and Neuropathology, Brain Research Institute, Niigata University Awarded the degree of Ph.D.

Research and professional experience:

1995-1997	Special Postdoctoral Researcher in Frontier Research Program, RIKEN
1997-1998	Special Postdoctoral Researcher in RIKEN Brain Science Institute

1998-2000	BSI Researcher in RIKEN Brain Science Institute
2000-2002	Senior Research Fellow, Tokyo Institute of Psychiatry
2002-2003	Acting Head of Department, Department of Molecular Psychiatry, Tokyo Institute of Psychiatry
2003-2005	Head of Department, Department of Molecular Psychiatry, Tokyo Institute of Psychiatry
2005-present	Director, Molecular Psychiatry Research Division of Psychobiology, Tokyo Institute of Psychiatry
(1995-2005)	Visiting Lecturer Brain Research Institute, Niigata University
(1997)	Visiting Professor University of Louis Pasteur STRASBOURG
(2000-2009)	Visiting Researcher RIKEN Brain Science Institute
(2004-present)	Adjunctive Professor Tokyo Metropolitan University

Awards:

2001	Japan Neuroscience Society Young Investigator Award
2004	Distinguished International Scientist Collaboration Program Award (National Institute on Drug Abuse, USA)
2006	Tokyo Metropolitan Organization for Medical Research President Award

Membership of academic societies:

Society for Neuroscience (USA) (SfN) (1996-present)
International Brain Research Organization (IBRO) (1996-present)
International Narcotics Research Conference (INRC) (1997-present)
College on Problems of Drug Dependence (CPDD) (2006-present)
International Drug Abuse Research Society (IDARS) (2006-present)
Japan Neuroscience Society (1996-present)
The Molecular Biology Society of Japan (1994-present)
Japanese Narcotics Research Conference (JNRC)
(1996-present; Executive member, 2006-present)
The Japanese Society of Neuropsychopharmacology
(2001-present; Councilor, 2004-present, Executive member, 2008-present)
The Japanese Forum on Nicotine and Drug Dependence Studies
(2002-present; Councilor, 2005-present, Executive member, 2008-present)
Japanese Association for Study of Pain (2008-present)

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